

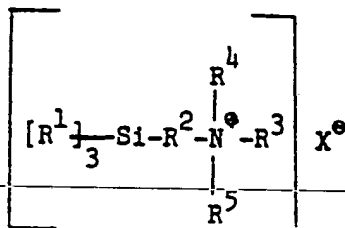


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<p>(21) International Application Number: PCT/US78/00255</p> <p>(22) International Filing Date: 28 December 1978 (28.12.78)</p> <p>(31) Priority Application Number: 865,707</p> <p>(32) Priority Date: 29 December 1977 (29.12.77) 29 Dec</p> <p>(33) Priority Country: US</p> <p>(71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY; 3M Center, P.O. Box 33427, St. Paul, MN 55133, United States of America.</p>	<p>(72) Inventors: WEN, Richard, Y.; 1900 Fredeen Court, New Brighton, MN 55112, United States of America. LaFLEUR, Linda, L.; 4982 North Greenwich Trail, Oakdale, MN 55109, United States of America. ENGLE, Michael, R.; 3850 White Bear Avenue, White Bear Lake, MN 55110, United States of America. LUCAS, Anthony J.; 10 Glenview Drive, Harvard, MA 01451, United States of America.</p> <p>(74) Agents: ALEXANDER, Cruzan; SELL, Donald, M.; LILLY, James, V.; P.O. Box 33427, St. Paul, MN 55133, United States of America.</p> <p>(81) Designated States: BR, CH (European patent), DE (European patent), GB (European patent), JP, SE (European patent), SU.</p> <p>Published with: International search report</p>	

(54) Title: COMPOSITIONS AND METHODS FOR INHIBITING PLAQUE FORMATION

(57) Abstract

A dentifrice composition which inhibits plaque formation over an extended period of time. Said composition contains an effective amount of plaque-inhibiting quaternary organosiloxane of the formula



wherein  $\text{R}^1$  is an alkoxy group having from 1 to 5 carbon atoms,  $\text{R}^2$  is an alkylene group having from 1 to 25 carbon atoms and  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are, individually, alkyl groups of from 1 to 25 carbon atoms, and X is an anion and iodine.

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## DESCRIPTION

Compositions and Methods for  
Inhibiting Plaque FormationTechnical Field

This invention relates to compositions and methods useful in inhibiting the growth of cariogenic bacteria and the formation of plaque on teeth in an oral environment.

5 The prevention of the formation of dental plaque is a highly desired result. Dental plaque results when cariogenic bacteria (e.g., Streptococcus Mutans) collect in colonies on the surface of teeth and form a tenacious deposit thereon. The presence of both the bacteria and the deposits is extremely  
10 detrimental to the health of the teeth because if the bacteria and plaque formation are not checked they may result in infected gingival tissue, the formation of dental caries and periodontal disease. In extreme cases they may ultimately result in the loss of teeth.

15 Background Art

Many attempts have been made to control cariogenic bacteria and plaque formation on teeth. For example, treatment with fluoride solutions or gels have been used to render the tooth enamel more resistant to the acid action caused by plaque.  
20 These treatments are typically performed in a dental office at periodic, but not frequent, intervals. Such treatments do not, however, result in plaque control for an extended period.

Even when the frequency of application of such treatments is increased only partial control has been shown. For example,  
25 studies wherein a fluoride-containing solution (1% fluoride concentration) was applied four to five times in the course of a year demonstrated only limited success due to the rapid re-



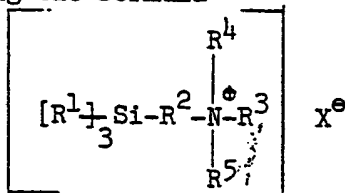
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establishment of plaque in the oral cavity. Additionally, the daily application of a fluoride gel by means of a custom-fitted vinyl mouthpiece for a period of twenty-one months showed no substantial change in plaque formation among treated and untreated patients. See "Clinical Anicaries Effect of Repeated Topical Sodium Fluoride Application by Mouthpiece", Journal of the American Dental Association, V. 75, No. 3, September, 1967, pp. 638-644.

Other attempts at inhibiting the formation of plaque have also been made. For example, U.S. Pat. No. 3,733,399 describes toothpaste compositions which contain the enzyme invertase as the active ingredient. Another approach is disclosed in U.S. Pat. No. 3,894,147 wherein the application to teeth of a dialkyl pyrophosphate having from about 8 to 14 carbon atoms in the alkyl groups is described as useful in inhibiting plaque formation. However, these approaches require frequent (e.g., daily) use, in order to effectively control the cariogenic bacteria and inhibit the formation of plaque over an extended period of time.

## 20 Disclosure of Invention

In accordance with the present invention there is provided a dentifrice composition which contains a quaternary ammonium organosiloxane having the formula



25 wherein  $\text{R}^1$  is an alkoxy group having from 1 to 5 carbon atoms,  $\text{R}^2$  is an alkylene group having from 1 to 25 carbon atoms, and  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are, individually, alkyl groups of from 1 to 25 carbon atoms, and X is an anion, preferably selected from chlorine, bromine, fluorine and iodine. Preferably, compositions of the invention contain at least about 0.05% by weight,

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and most preferably from about 0.25% to 1% by weight, of the quaternary ammonium organosiloxane.

In another embodiment of the present invention there is provided a method for inhibiting plaque formation which comprises contacting teeth with an effective amount of the above-described composition.

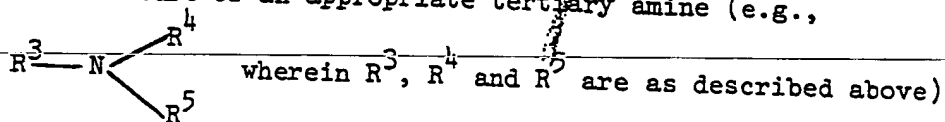
As it is used throughout this specification the term "dentifrice" refers to compositions for topical application to the teeth. Representative of such compositions are mouthwashes or rinses, toothpastes, toothpowders, gels, etc.

The present invention provides compositions and processes which are useful in controlling cariogenic bacteria and inhibiting the formation of plaque over an extended period of time despite relatively infrequent application of the compositions to teeth.

#### Best Mode for Carrying Out the Invention

The dentifrice compositions of the invention may be applied to the teeth by techniques such as painting or brushing, spraying, bathing and rinsing. Other means of application are also possible and will be obvious to those in the art as a result of this disclosure. After application to the teeth it is preferred that a short period of time (e.g., one minute) pass before the user eats or drinks.

The organosiloxanes useful in the present invention are known materials that may be prepared by simply agitating a warm mixture of an appropriate tertiary amine (e.g.,

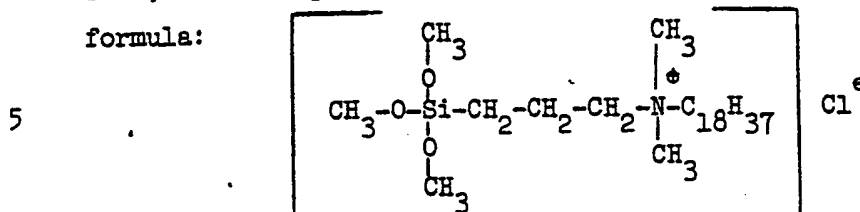


and an appropriate silane (e.g.,  $[\text{R}^1]_3\text{-Si-R}^2\text{X}$  where  $\text{R}^1$ ,  $\text{R}^2$  and X are as described above).

In the present invention it is preferred that  $\text{R}^1$  be a methoxy group (i.e.,  $\text{CH}_3\text{O-}$ );  $\text{R}^2$  be an alkylene group having 1 to 10 carbon atoms (most preferably a propylene group, i.e.,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ );  $\text{R}^3$  be an alkyl group having from 10 to 20

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carbon atoms (most preferably an octadecyl group, i.e.,  $C_{18}H_{37}$ );  $R^4$  and  $R^5$  each be methyl groups (i.e.,  $CH_3$ -) and X be chlorine. Thus, the most preferred siloxane may be represented by the formula:



This compound may also be referred to as 3-(trimethoxysilyl)-propyl-dimethyloctadecyl ammonium chloride. It may be obtained from Dow Corning Corporation as "Q9-5700" as a 50% by weight solution of the siloxane in methanol.

10 When provided in solution form, dentifrices of the present invention typically comprise a solution of the organosiloxane in water or a mixture of water and an alcohol. Typically the alcohol is a lower, non-toxic alkanol (e.g., ethanol, propanol, etc.). Liquid solutions of the siloxane are particularly use-  
15 ful in mouthwashes or rinses.

A variety of other ingredients may be added to the dentifrices of the present invention. Thus, for example, prophylactic agents (e.g., supplemental caries-preventing aids) may be included. Moreover, polishing agents, soaps or detergents,  
20 flavoring and sweetening agents, thickening agents and humectants may also be included. Preferably these other ingredients are free from polyvalent metal such as calcium and magnesium.

Representative of suitable prophylactic agents are sodium fluoride, stannous fluoride, potassium fluoride, hexylamine  
25 hydrofluoride, myristylamine hydrofluoride, betaine fluoride, glycine potassium fluoride, etc. A particularly preferred prophylactic agent is sodium fluoride. Typically the fluoride prophylactic agents are present in sufficient concentration so as to provide an available fluoride ion concentration of up to  
30 about 2% by weight, and preferably in the range of about 0.5-2% by weight, of the dentifrice composition.

Representative of suitable polishing agents are abrasive

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materials such as insoluble condensed phosphates such as calcium pyrophosphate, insoluble calcium polyphosphate (also known as calcium polymetaphosphate) and highly polymerized sodium polyphosphate (also known as sodium polymetaphosphate); and water-  
5 impervious cross-linked thermosetting resins such as the condensation products of melamine and urea with formaldehyde. Other suitable polishing agents will be obvious to those skilled in the art as a result of this disclosure.

Preferably the polishing agent is not so abrasive so as to  
10 scratch or unduly abrade the tooth surface or the dentin. Rather it only cleans the tooth surface. The polishing agents may comprise up to 95% by weight of the dentifrice composition.

Representative of suitable soaps or detergents are the soaps of high molecular weight fatty acids such as sodium and potassium soaps of myristic, stearic palmitic acids and fatty acid  
15 mixtures of palm oil and coconut oil. Typical useful synthetic detergents include alkyl sulfates and sulfonates having alkyl groups of from about 8 to 18 carbon atoms, such as sodium lauryl sulfate, the sulfated fatty alcohols derived from  
20 coconut oil and palm oil, etc. These materials may comprise up to about 5% by weight of the dentifrice composition.

Representative of suitable flavoring and sweetening agents are the oils of wintergreen, peppermint, spearmint, sassafras and anise. Additionally small amounts of sweetening agents  
25 such as saccharin, dextrose, levulose, etc. may also be employed. These flavoring and sweetening agents may comprise up to about 5% by weight of the dentifrice composition.

Representative of suitable gelling or thickening agents are water-soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxy methyl hydroxy ethyl  
30 cellulose; natural gums such as gum karaya, gum arabic, and gum tragacanth; and colloidal magnesium-aluminum silicate or finely divided silica. Such thickening agents may comprise up to about 5% by weight of the dentifrice composition.



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Representative of suitable humectants are glycerine, sorbitol, other polyhydric alcohols. The humectants may comprise up to about 35% by weight of the dentifrice composition.

Tests which demonstrate the effectiveness of the present invention in inhibiting the growth of plaque were performed on Rhesus Monkeys. The teeth of the monkeys were clinically preconditioned to a plaque-free state by ultrasonic cleaning and subsequent dental prophylaxis using a soft rubber prophylaxis cup and standard pumice-filled prophylaxis paste. The teeth were then treated in various fashions and the effect of the treatment upon the formation of plaque was observed.

The effectiveness of plaque inhibition was measured by means of a plaque index number. Plaque index was determined by applying erythrosine B dye (FD&C Red dye #3, Color Index No. 45430) to the teeth. This dye stains plaque but not tooth enamel. The stained plaque was visually observed and assigned a rating number using the following scale.

	0	No plaque
20	0.25	Light plaque covering about 1/4 of tooth surface
	0.5	Light plaque covering about 1/2 of tooth surface
	0.75	Light plaque covering about 3/4 of tooth surface
25	1.0	Light plaque covering entire tooth surface
	1.25	Heavy plaque on 1/4 of tooth surface, light plaque on remainder
	1.50	Heavy plaque on 1/2 of tooth surface, light plaque on remainder
30	1.75	Heavy plaque on 3/4 of tooth surface, light plaque on remainder
	2.0	Heavy plaque on entire tooth surface

The plaque was observed visually and rated periodically for the duration of the test. The ratings for each monkey were then averaged to obtain the reported plaque index for each monkey.





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A solution containing 3-(trimethoxysilyl)-propyldimethyloctadecylammoniumchloride ("Q9-5700") was applied to the upper incisors of the test monkeys. Solution A comprised 50% "Q9-5700" and 50% methanol by weight. Solutions B & C each comprised 1% "Q9-5700", 1% methanol and 98% deionized water by weight. Different lots of "Q9-5700" were employed in Solutions B & C. The untreated teeth of the monkeys served as a control. They received no preventative treatment during the tests.

The monkeys were fed twice a day with a diet which encouraged plaque formation. The diet consisted of about 135 grams of Purina<sup>®</sup> New World Monkey Chow<sup>®</sup> which had been softened with 200 milliliters of distilled water and to which 118 grams of sugar had been added. The Monkey Chow<sup>®</sup> is commercially available from Ralston Purina Co. and has a guaranteed analysis of

Crude protein not less than	25.0%
Crude fat not less than	5.0%
Crude fiber not more than	3.5%
Added minerals not more than	3.0%
Ash not more than	6.0%

The ingredients in the Monkey Chow<sup>®</sup> were ground yellow corn, soybean meal, ground wheat, corn gluten meal, dried skimmed milk, animal fat preserved with BHA, sucrose, brewers' dried yeast, salt, dehydrated alfalfa meal, vitamin B<sub>12</sub> supplement, riboflavin supplement, calcium pantothenate, niacin, choline chloride, menadione sodium bisulfite (source of vitamin K activity), folic acid, pyridoxine hydrochloride, thiamin, ascorbic acid, vitamin A supplement, D activated animal sterol (source of vitamin D<sub>3</sub>), vitamin E supplement, iron oxide, iron sulfate, manganese sulfate, calcium iodate, calcium carbonate, dicalcium phosphate, manganous oxide, copper oxide, cobalt carbonate, zinc oxide.

The results of the tests are as set forth in the following table:

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MONKEY#	SOLUTION	TREATMENT	# OF DAYS TEST LENGTH	PLAQUE INDEX	
				TREATED TEETH	CONTROL TEETH
5	A	1	14	.270	1.58
	B	1	14	.35	1.25
	C	1	12	.50	1.00
	C	2	12	.187	1.312
	C	3	12	.281	1.437
10	C	4	12	.56	1.437
	C	1	12	1.625	1.75
	C	5	9	.312	>2.0
	C	2	9	.375	1.875

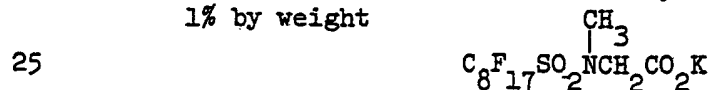
TREATMENT

15 1. On day 1 the solution was brushed onto the teeth with a paint brush and air dried for 2 minutes. There was no further treatment for duration of the test.

2. The teeth were brushed daily with the solution.

20 3. On day 1 the solution was brushed onto the teeth with a paint brush, air dried for 2 minutes. Thereafter the treated teeth were brushed daily with deionized water.

4. On day 1 the solution was brushed onto the teeth with a paint brush, air dried for 2 minutes. Thereafter the treated teeth were brushed daily with a composition of 1% by weight



in deionized water.

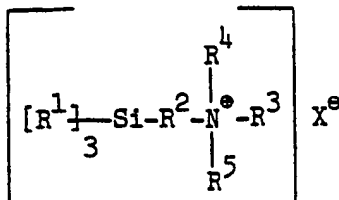
5. The teeth were rinsed daily with lcc of the solution.

30 Monkey 6 salivated excessively. Hence the single application of Solution C was rinsed away. However, when Solution C was later applied to the same monkey each day for 9 days it provided effective plaque control. Similar plaque control is achieved when the methanol employed in the solutions is removed or is replaced with a non-toxic alcohol such as ethanol.

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CLAIMS

1. A dentifrice composition which contains a quaternary ammonium organosiloxane having the formula



5 wherein  $\text{R}^1$  is an alkoxy group having from 1 to 5 carbon atoms,  $\text{R}^2$  is an alkylene group having from 1 to 25 carbon atoms and  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are, individually, alkyl groups of from 1 to 25 carbon atoms, and X is an anion.

- 10 2. A dentifrice composition in accordance with claim 1 wherein X is selected from chlorine, bromine, fluorine and iodine.

3. A dentifrice composition according to claim 2 wherein said composition contains at least about 0.05% by weight of said quaternary ammonium organosiloxane.

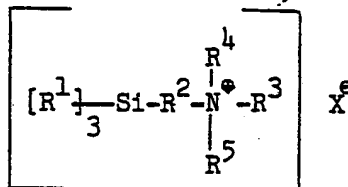
- 15 4. A dentifrice composition according to claim 3 wherein  $\text{R}^1$  is methoxy,  $\text{R}^2$  is an alkylene group having from 1 to 10 carbon atoms,  $\text{R}^3$  is an alkyl group having from 10 to 20 carbon atoms,  $\text{R}^4$  and  $\text{R}^5$  are, individually, methyl groups, and X is chlorine.

- 20 5. A dentifrice composition according to claim 4 wherein  $\text{R}^2$  is a propylene group and  $\text{R}^3$  is an octadecyl group.

6. The method of inhibiting plaque formation by contacting teeth with an effective amount of a dentifrice composition

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which contains a quaternary ammonium organosiloxane compound having the formula



wherein  $\text{R}^1$  is an alkoxy group having from 1 to 5 carbon atoms,  $\text{R}^2$  is an alkylene group having from 1 to 25 carbon atoms, and  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are, individually, alkyl groups of from 1 to 25 carbon atoms, and X is an anion.

7. The method of claim 6 wherein X is selected from chlorine, bromine, fluorine and iodine.
- 10 8. The method of claim 7 wherein  $\text{R}^1$  is methoxy,  $\text{R}^2$  is an alkylene group having from 1 to 10 carbon atoms,  $\text{R}^3$  is an alkyl group having from 10 to 20 carbon atoms,  $\text{R}^4$  and  $\text{R}^5$  are, individually, methyl groups, and X is chlorine.
- 15 9. The method of claim 8 wherein  $\text{R}^2$  is a propylene group and  $\text{R}^3$  is an octadecyl group.
10. The method of claim 6 wherein said teeth are contacted by a composition comprising at least about 0.05% by weight of said quaternary ammonium organosiloxane compound.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US78/00255

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *			
According to International Patent Classification (IPC) or to both National Classification and IPC			
Int. Cl.	A 61 K	7/22	A 61 K 31/695 A61K/31/14
U.S. Cl.	424/54	424/184	424/329
<b>II. FIELDS SEARCHED</b>			
Minimum Documentation Searched *			
Classification System	Classification Symbols		
U.S.	424/54	424/184	424/329
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *			
Chemical Abstracts-"Dentifrices" "Quaternary Ammonium Compounds" - "Siloxanes and Silicones"			
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> 14			
Category *	Citation of Document, 15 with indication, where appropriate, of the relevant passages 17		Relevant to Claim No. 18
X	U.S., A, 3,624,120 Published 30 November 1971 Yetter		1 to 10
A	U.S., A, 2,580,473 Published 1 January 1952 Sowa et al		1 to 5
X	U.S., A, 3,507,955 Published 21 April 1970 Osipow		1 to 10
A	U.S., A 2,806,814 Published 17 September 1957 Richter		1 to 10
A	U.S., A 3,297,452 Published 10 January 1967 Wing et al		1 to 10
A	U.S., A 3,703,583 Published 21 November 1972 Martin		1 to 10
A	U.S., A 3,124,512 Published 10 March 1964 Schmid et al		1 to 10
A	U.S., A 2,921,885 Published 19 January 1960 Bouchal		1 to 10
<p>* Special categories of cited documents: 16</p> <p>"A" document defining the general state of the art</p> <p>"E" earlier document published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance</p>			
<b>IV. CERTIFICATION</b>			
Date of the Actual Completion of the International Search *		Date of Mailing of this International Search Report *	
30 March 1979		19 APR 1979	
International Searching Authority *		Signature of Authorized Officer **	
ISA/US		Shep K. Roe	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET  
(Not for publication)

- X N Chemical Abstracts Volume 50 No. 7 1-5  
issued April 10, 1956 (Columbus, Ohio,  
U.S.A.) Ralph K. Iler "Quaternary  
Ammonium Organosiloxanates and their  
Applications" U.S. 2,721,812, October 25, 1955,  
the abstract No. 50: S313C
- X N Chemical Abstracts Volume 55 No. 14 1-5  
issued July 10, 1961 (Columbus, Ohio,  
U.S.A.) Edward L. Morehouse "Organosil-  
icon Salts Containing Aminoalkylsilyl  
groups" U.S. 2,972,598 February 21, 1961,  
the abstract No. 55: 13315C
- A N, Accepted Dental Therapeutics, 35th, Ed. 1-10  
(1973) published by American Dental  
Association, 211 E. Chicago Ave. Chicago, Ill.  
60611, pages 55, 60-64, 193-194, 253-258,  
264-266.